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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

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Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 03/089429 A1

(54) Title: PROCESS FOR 5-[[2(R)-[1(R)-[3,5-BIS(TRIFLUOROMETHYL)PHENYL]ETHOXY]-3(S)-(4-FLUOROPHENYL)-4-MORPHOLINYL]METHYL]-1,2-DIHYDRO-3H-1,2,4-TRIAZOL-3-ONE

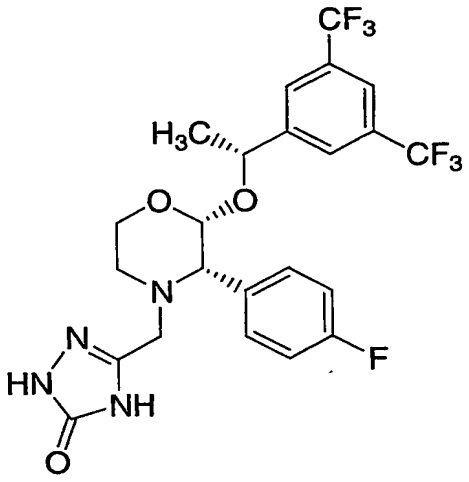
(57) Abstract: The present invention is concerned with a novel process for the preparation of the compound 5-[[2(R)-[1(R)-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3(S)-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro-3H-1,2,4-triazol-3-one. This compound is useful as a substance P (neurokinin-1) receptor antagonist. In particular, the compound is useful e.g., in the treatment of psychiatric disorders, inflammatory diseases and emesis.

TITLE OF THE INVENTION

PROCESS FOR 5-[[2(R)-[1(R)-[3,5-BIS(TRIFLUOROMETHYL)PHENYL] ETHOXY]-3(S)-(4-FLUOROPHENYL)-4-MORPHOLINYL]METHYL]-1,2-DIHYDRO-3H-1,2,4-TRIAZOL-3-ONE

BACKGROUND OF THE INVENTION

The present invention relates to processes for the preparation of 5-[[2(R)-[1(R)-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3(S)-(4-fluorophenyl) -4-morpholinyl]methyl]-1,2-dihydro-3H-1,2,4-triazol-3-one, aprepitant,

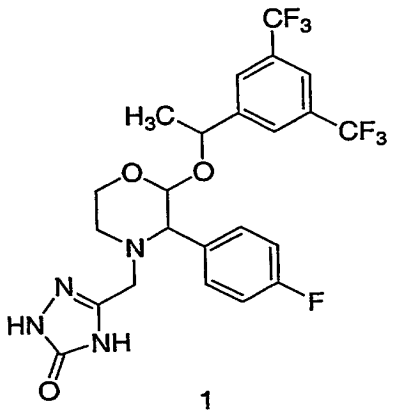


which is a useful therapeutic agent, specifically as a substance P (neurokinin-1) receptor antagonist. This compound is disclosed as having therapeutic utility in U.S. Patent No. 5,719,147.

U.S. Patent Nos. 5,637,699, 6,096,742, 6,229,010 and 6,297,376 relate to processes of manufacture and the discovery of polymorphic forms of this compound. In contrast to previously known processes, the present invention provides a more practical and economical method for preparing the compound in relatively high yield and purity. As such, there is a need for a process for the preparation of the compound that is cost-effective and utilizes readily available reagents.

SUMMARY OF THE INVENTION

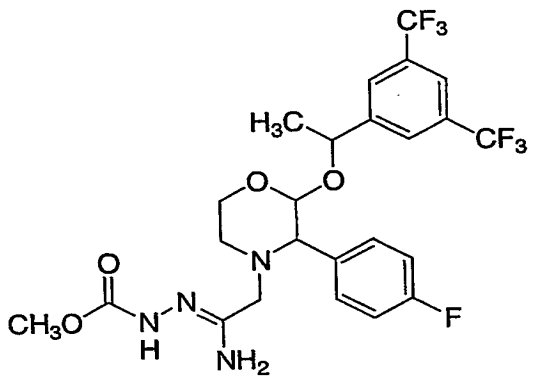
The present invention relates to a process for preparing a compound of formula 1:



1

comprising:

cyclizing a compound of formula 4:



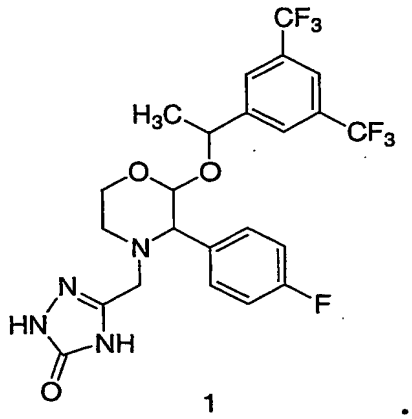
4

at a temperature of 140-150°C to produce the compound of formula 1.

In particular, such compounds are substance P (neurokinin-1) receptor antagonists which are useful, e.g., in the treatment of psychiatric disorders, inflammatory diseases and emesis.

DETAILED DESCRIPTION OF THE INVENTION

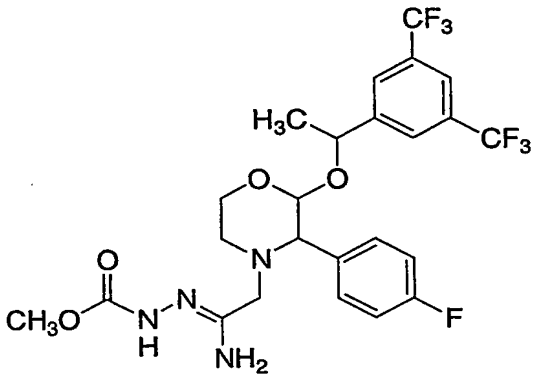
The present invention relates to a process for preparing a compound of formula 1:



1

The process comprises :

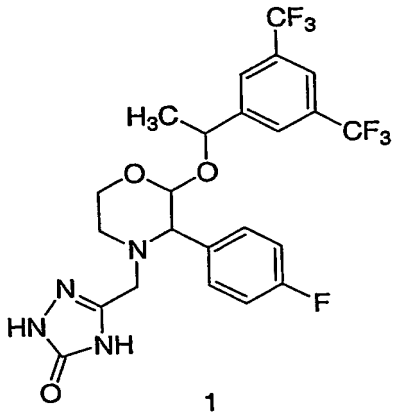
cyclizing a compound of formula 4:



4

at a temperature of 140-150°C to produce the compound of formula 1.

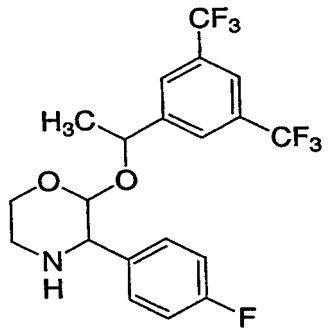
More particularly, the present invention is directed to processes for the preparation of a compound of formula 1:



1

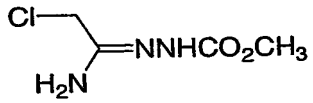
The processes are comprised of:

(a) reacting the hydrochloride salt of a compound of formula 2:



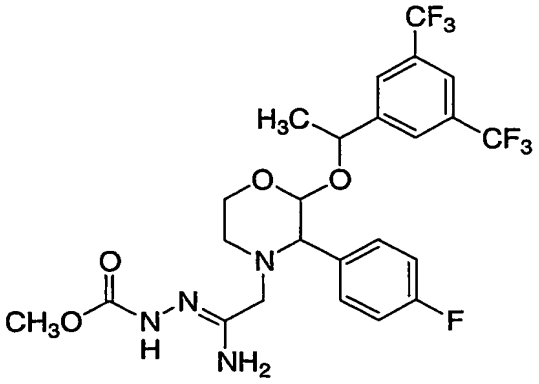
2

in the presence of an inorganic base and toluene with a compound of the formula 3:



3

to produce the compound of formula 4:

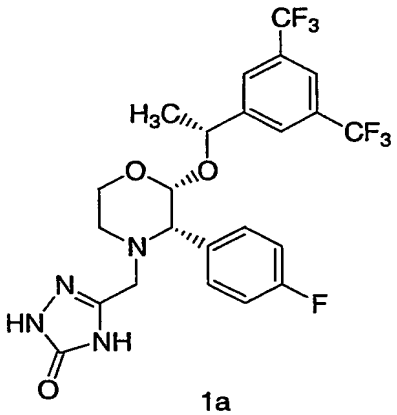


4 ;

(b) washing with an aqueous phase, and

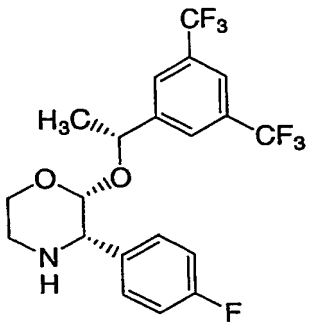
(c) cyclizing at a temperature of 140-150°C to produce the compound of formula 1.

Even more particularly, a process for preparing a compound of formula 1a:



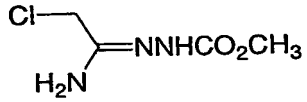
1a

is disclosed wherein the hydrochloride salt of a compound of formula 2a:



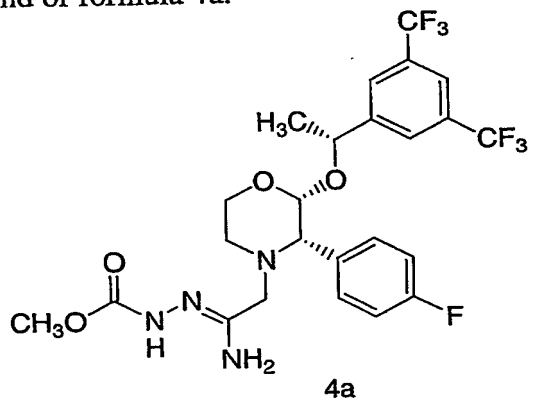
2a

is reacted in the presence of an inorganic base and toluene with a compound of the formula 3:



3

to produce the compound of formula 4a:



4a ;

(b) washing with an aqueous phase and

(c) cyclizing at a temperature of 140-150°C to produce the compound of formula 1a.

The washing step described herein typically uses an aqueous phase, e.g., water, and may optionally contain a salt. Representative examples of salts that are useful herein include KCl, $KHCO_3$, K_2CO_3, Na_2CO_3, $NaHCO_3$, NaCl and similar such salts. KCl is the preferred salt.

In another aspect of the invention, the process is further comprised of a drying step prior to cyclization.

As used herein the term "inorganic base" refers to compounds such as sodium carbonate, cesium carbonate, sodium hydroxide, potassium hydroxide, potassium carbonate and the like. More particularly, the preferred inorganic base is potassium carbonate.

More particularly, the present invention relates to the process described above wherein compound 2 or 2a is reacted with compound 3 in the presence of an inorganic base, toluene and a polar aprotic solvent. As used herein, the term "polar aprotic solvent" refers to a solvent that neither donates or accepts protons, and is, for example, selected from the group consisting of: dimethylformamide (DMF), dimethylsulfoxide (DMSO), N-methylpyrrolidone (NMP), acetonitrile (MeCN), N,N-dimethylacetamide (DMAC) and hexamethylphosphoramide (HMPA).

The process described herein is surprisingly efficient, minimizing the production of a mixture of isomers, and thus increasing productivity and purity. The subject process also minimizes the use of toxic solvents.

The 2-[1-[3,5-bis(trifluoromethyl)phenyl]ethoxy-3-(4-fluorophenyl)-1,4-oxazine starting material 2 and (2R, 2-alpha-R, 3a)-2-[1-[3,5-bis(trifluoromethyl)-phenyl]ethoxy-3-(4-fluorophenyl)-1,4-oxazine starting material 2a may be obtained in accordance with PCT WO 01/94324 A1 (published December 13, 2001) and US 2002/0052494 A1 (published May 2, 2002), or using modifications thereof. The starting material may be used directly or following purification. Purification procedures include crystallization, distillation, normal phase or reverse phase chromatography. The following example is provided for purposes of illustration and is not intended to limit the disclosed invention.

EXAMPLE 1

[2*R*-[2α(*R**),3α]]-5-[[2-[1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro-3*H*-1,2,4-triazol-3-one

A mixture of the starting material as the hydrochloride salt of (2R, 2-alpha-R, 3a)-2-[1-[3,5-bis(trifluoromethyl)phenyl]ethoxy-3-(4-fluorophenyl)-1,4-oxazine (2a) (1.00 kg; 2.11 mol) and potassium carbonate (1.02 kg; 7.39 mol) in DMSO (2.2 L) and toluene (1.0 L) was cooled to 15°C. A slurry of amidrazone 3 (367 g; 2.22 mol) in toluene (1.5 L) was added. The mixture was stirred and then partitioned between toluene (4.0 L) and water (5.0 L). The phases were separated at 40°C. The organic layer (containing 4a) was washed with water (5.0 L) at 40°C and

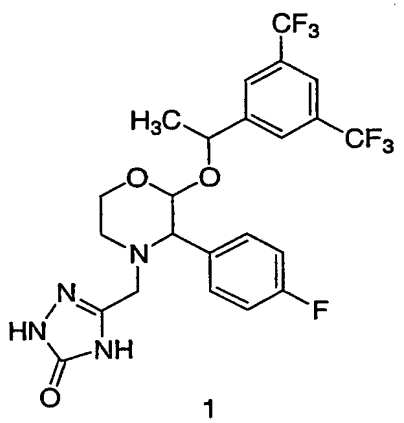
then partially concentrated at atmospheric pressure, providing intermediate 4a, which is used in the next step without isolation. The resulting solution containing intermediate 4a was heated to 140°C for 3 h and then allowed to cool to RT. The solids were filtered and dried *in vacuo* at 40 °C. The product (1.00 kg) was dissolved in methanol (10.0 L) and 50 g of Darco was added. The mixture was heated at 60°C for 1 h and then filtered at this temperature. The filtrates were allowed to cool slowly to RT. Water (5.0 L) was added slowly over 1 h. The slurry was cooled to 5 °C and the solids were filtered and dried *in vacuo* at 40 °C to yield 0.96 kg (85% overall yield) of the product [2*R*-[2α(*R**),3α]]-5-[[2-[1-[3,5-bis(trifluoromethyl)phenyl]-ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro-3*H*-1,2,4-triazol-3-one (i.e. 5-[[2(R)-[1(R)-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3(S)-(4-fluorophenyl) -4-morpholinyl]methyl]-1,2-dihydro-3H-1,2,4-triazol-3-one).

Intermediate 4a: $[\alpha]_D^{25}$ = +84° (c=1.02, methanol); ^{1}H NMR (400 MHz, CDCl3) δ 7.64 (s, 2H), 7.34 (br t, *J* ~ 7, 2H), 7.16 (s, 1H), 7.03 (t, *J* = 8.4, 2H), 5.8 (very br s, 2H), 4.88 (q, *J* = 6.6, 1H), 4.33 (d, *J* = 2.8, 1H), 4.24 (td, *J* = 11.6, 2.0, 1H), 3.77 (s, 2H), 3.66 (ddd, *J* = 11.6, 3.2, 1.6, 1H), 3.46 (d, *J* = 2.8, 1H), 3.31 (d, *J* = 14.5, 1H), 2.96 (br d, *J* = 11.6, 1H), 2.59 (d, *J* = 14.5, 1H), 2.50 (td, *J* = 12.1, 3.2, 1H), 1.47 (d, *J* = 6.6, 3H). Anal. Calc. for $C_{24}H_{25}F_7N_4O_4$: C, 50.89; H, 4.45; F, 23.48; N, 9.89. Found: C, 50.48; H, 4.40; F, 23.43; N, 9.84. Final product 1a: Mp: 255 °C; $[\alpha]_D^{25}$ = +69° (c=1.00, methanol); ^{1}H NMR (400 MHz, CD_3OD) δ 7.70 (s, 1H), 7.51 (m, 2H), 7.32 (s, 2H), 7.04 (t, *J* = 8.7, 2H), 4.94 (q, *J* = 6.3, 1H), 4.35 (d, *J* = 2.8, 1H), 4.28 (td, *J* = 11.5, 2.8, 1H), 3.66 (ddd, *J* = 11.5, 3.3, 1.6, 1H), 3.54 (d, *J* = 14.3, 1H), 3.48 (d, *J* = 2.8, 1H), 2.88 (br d, *J* = 11.9, 1H), 2.86 (d, *J* = 14.3, 1H), 2.49 (td, *J* = 11.9, 3.6, 1H), 1.44 (d, *J* = 6.3, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 164.1 (d, *J* = 245.9), 158.7, 147.6, 147.0, 134.1 (d, *J* = 3.1), 132.7 (d, *J* = 33.4), 132.4 (d, *J* = 8.0), 127.8 (m), 124.6 (q, *J* = 272.0), 122.3 (m), 116.1 (d, *J* = 21.6), 97.1, 73.7, 70.5, 60.4, 53.6, 52.2, 24.7. Anal. Calc. for $C_{23}H_{21}F_7N_4O_3$: C, 51.69; H, 3.96; F, 24.88; N, 10.48. Found: C, 51.50; H, 3.82; F, 24.73; N, 10.44. HRMS: 534.1480 (meas.); 534.1502 (calc. for $C_{23}H_{21}F_7N_4O_3$).

All patents and patent publications cited herein are incorporated by reference in their entirety. While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various adaptations may be made without departing from the spirit and scope of the invention.

WHAT IS CLAIMED IS:

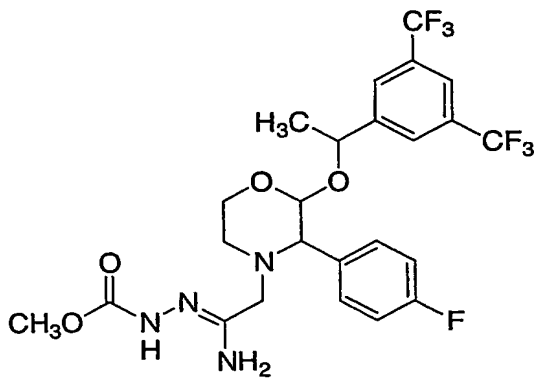
1. A process for preparing a compound of formula 1:



1

comprising:

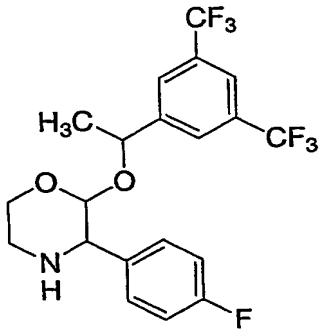
cyclizing a compound of formula 4:



4

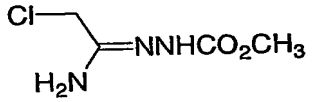
at a temperature of 140-150°C to produce the compound of formula 1.

2. The process of Claim 1 which further comprises reacting the hydrochloride salt of a compound of formula 2:



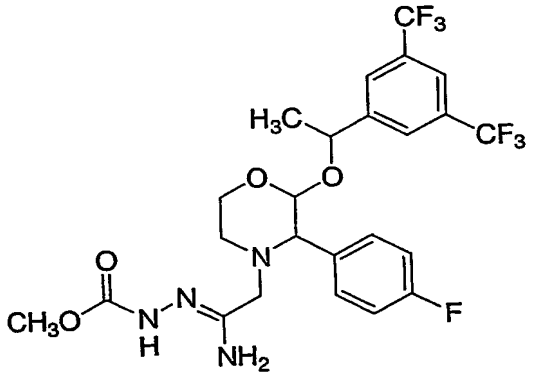
2

in the presence of an inorganic base and toluene with a compound of the formula 3:



3

to produce the compound of formula 4:



4

3. The process of Claim 2 wherein the compound of formula 2 is reacted with the compound of formula 3 in the presence of an inorganic base, toluene and a polar aprotic solvent.

4. The process of Claim 3 wherein the polar aprotic solvent is selected from the group consisting of: dimethylformamide, dimethylsulfoxide, N-methylpyrrolidone, acetonitrile, N,N-dimethylacetamide and hexamethylphosphoramide.

5. The process of Claim 4 wherein the polar aprotic solvent is dimethylformamide or dimethylsulfoxide.

6. The process of Claim 1 further comprising washing the compound of formula 4 prior to cyclization with an aqueous phase.

7. The process of Claim 6 wherein the aqueous phase comprises an aqueous salt solution.

8. The process of Claim 5 wherein the aqueous salt solution contains at least one compound selected from the group consisting of: KCl, $KHCO_3$, K_2CO_3, Na_2CO_3, $NaHCO_3$ and NaCl,

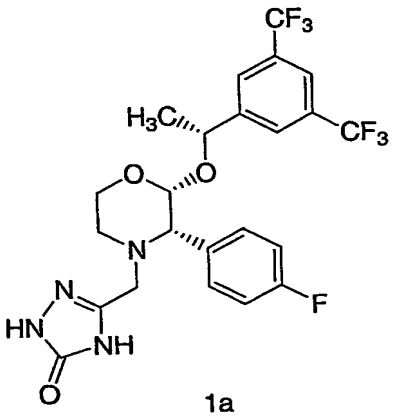
9. The process of Claim 8 wherein the aqueous salt solution contains KCl.

10. The process of Claim 1 further comprising drying prior to cyclization.

11. The process of Claim 2 wherein the inorganic base is selected from the group consisting of: sodium carbonate, cesium carbonate, sodium hydroxide, potassium hydroxide and potassium carbonate.

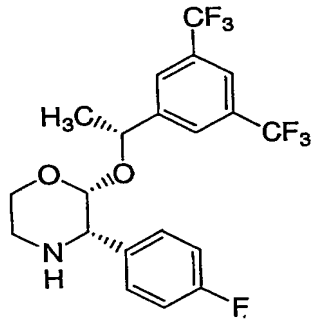
12. The process of Claim 7 wherein the inorganic base is potassium carbonate.

13. The process of Claim 1 wherein the compound of formula 1 is of the formula 1a:



1a

14. The process of Claim 2 wherein compound 2 is a compound of the formula 2a:



2a

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/11956

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C07D 413/06
US CL : 544/132

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 544/132

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 6,096,742 A (CROCKER et al) 01 August 2000 (01.08.2000), column 136, Ex. 105.	2-5,8,9,11 and 14

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 July 2003 (10.07.2003)	30 JUL 2003
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703)305-3230	Authorized officer Robert W. Ramsuer Telephone No. 703-308-1235

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

Inter[redacted]al application No.
PCT/US03/11956

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claim Nos.: 1,6,7,10,12 and 13
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
The claims do not provide a sufficient description of subject matter upon which a reasonable search may be preformed.

3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.